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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/218,481	12/22/98	VAN BRUGGEN	N 11669.41US01

HM22/0605

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EXAMINER	
UNGAR, S	
ART UNIT	**PAPER NUMBER**
1642	10

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/218,481	Applicant(s) Van Bruggen et al
	Examiner Ungar	Group Art Unit 1642

☒ Responsive to communication(s) filed on *Mar 13, 2000* .

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-6, 8-22, and 24-29* is/are pending in the application.

Of the above, claim(s) *3-6, 11-21, and 27-29* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1, 2, 8-10, 22, and 24-26* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *5*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

1. The Election filed March 13, 2000 (Paper No. 8) in response to the Office Action of December 7, 1999 (Paper No. 6) is acknowledged and has been entered. Claims 1-6, 8-22 and 24-29 are pending in the application, claims 7 and 23 have been canceled and claims 1 and 22 have been amended. Claims 3-6, 11-21 and 27-29 have been withdrawn from further consideration by the examiner under 37 CAR 1.142(b) as being drawn to non-elected inventions. Claims 1, 2, 8-10, 22 and 24-26 are currently under prosecution.

2. Applicant's election of Group I, claims, 2, 8-10, 22 and 24-26 in Paper No 8 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP 818.03(a). Applicant's election, with traverse, of the species of monoclonal antibody in Paper No. 8 is acknowledged. The traversal is on the ground(s) that search of all of the species would not impose a serious burden on the examiner. This is found persuasive and the restriction requirement drawn to species of antibodies is withdrawn.

Specification

3. The Brief Description of the Drawings is objected to because Figure 1 reveals panels 1a and 1b, however, the Brief Description of Figure 1 does not describe each of the panels; Figure 3 reveals panels 3a and 3b, however, the Brief Description of Figure 3 does not describe each of the panels; Figure 12 reveals panels 12a and 12b, however, the Brief Description of Figure 12 does not describe each of the panels.

Claim Advisory

4. Applicant is advised that should claim 2 be found allowable, claim 22 will be rejected under 35 U.S.C. 101 as being a substantial duplicate thereof because claim 2 is dependent on claim 1 and includes all of the limitations of claim 1. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to reject the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claim Objections

5. Claims 8-10 are objected to because claim 8-10 are dependent upon canceled claim 7. The rejection can be obviated by amending the dependency of the claims to be dependent upon claim 1.

6. Claims 24-26 are objected to because claim 24-26 are dependent upon canceled claim 23. The rejection can be obviated by amending the dependency of the claims to be dependent upon claim 22.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> "The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention."

7. Claims 8 and 24 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 8 and 24 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treatment using chimeric antibodies wherein the antibodies are anti-VEGF murine antibodies which have human heavy and light constant chain domains in place of the homologous murine sequences, does not reasonably provide enablement for a method of treatment using chimeric antibodies. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The claims are drawn to a method of treating a mammal with a chimeric anti-VEGF antibody. This includes antibodies fused to non-immunoglobulin proteins as well as antibodies wherein any domain of the antibody is substituted by corresponding regions or residues of human antibodies including but not limited to CDR grafted antibodies. The specification teaches that chimeric forms of murine antibodies also are produced by substituting the coding sequence of selected human heavy and light constant chain domains in place of the homologous murine sequences (p. 13, lines 6-10) and that antibodies within the scope of the invention include variant antibodies, such as chimeric (including "humanized") antibodies. It is clear that the teachings in the specification are not limiting.

One cannot extrapolate the teaching of the specification to the scope of the claims because there is no guidance in the specification for the production of other types of fusion proteins which would fall into the category of "chimeric" antibody. Modification of the antibody in the formation of a chimeric recombinant molecule can affect the specificity and affinity of the antibody due to changes in three dimensional conformation of the variable region and it could not be predicted from the specification whether all types of "chimeric" antibodies would retain the ability to bind to antigenic determinants on VEGF, thus undue experimentation would be required by one skilled in the art to make chimeric antibodies commensurate in scope with the claimed invention using the instant specification for guidance.

8. Claims 1, 2, 8, 22 and 24 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 8 and 24 are indefinite because they recite the term "chimeric". The exact meaning of the word chimeric is not known. The term chimeric is generic to a class of antibodies which are products of genetic shuffling of antibody domains and other active proteins. The term encompasses antibodies fused to non-immunoglobulin proteins as well as antibodies wherein any domain of the antibody is substituted by corresponding regions or residues of human antibodies including but not limited to CDR grafted antibodies.

Claims 1, 2 and 22 are vague and indefinite because claims 1 and 22 do not contain a positive process step which clearly relates back to the preamble.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 1 and 8-10 are rejected under 35 U.S.C. § 102(b) as being anticipated by WO94/10202 as evidenced by as evidenced by Taber's Cyclopedic Medical Dictionary (1989, 16th Ed, F.A. Davis Company, Philadelphia, p.742) and Risau (Acta Neurochirurgica. Supplementum, 1994, 60:109-112).

In order to facilitate compact prosecution, it is assumed for examination purposes that claims 8-10 are dependent upon claim 1.

The claims are drawn to a method of treating a mammal having edema, comprising administering to said mammal an effective amount of hVEGF antagonist wherein said antagonist comprises an anti-VEGF antibody, wherein the antibody is a monoclonal antibody, a chimeric antibody, a humanized antibody.

Taber teaches that the term glioblastoma is synonymous with the term glioma (p. 742).

Risau teaches that VEGF expression is induced and strongly upregulated in human malignant glioblastoma and that this tumor is characterized by vascular proliferations, vascular leakage and edema (see abstract).

WO94/10202 teaches a method of treating a tumor comprising administering to the mammal a therapeutically effective amount of a hVEGF antagonist sufficient

to reduce the size of the tumor (claim 26) and teaches that within the scope of the invention antagonists include monoclonal antibodies that bind to hVEGF (p 4, lines 23-24) and variants of said monoclonal antibodies including chimeric and humanized variants of said monoclonal antibodies (p. 8, lines 13-27) and specifically teach that the invention is useful for treating glioblastoma and edema associated with brain tumors (p. 16, lines 25-37). It is noted that it is well known in the art that glioblastoma is a brain tumor and that glioblastoma is characterized by edema. Further, the reference exemplifies the treatment of and *in vivo* inhibition of glioma associated tumor growth in which anti-hVEGF monoclonal antibody was shown to inhibit tumor growth when compared to controls treated with either irrelevant antibody or PBS (p. 23, lines 1-23). It is noted that glioma is a synonym for glioblastoma. Although the reference does not specifically exemplify the treatment of edema, the method of the prior art comprises the same method steps as claimed in the instant invention, that is, administering an anti-hVEGF monoclonal antibody to a mammal that would be expected to have edema, thus the claimed method is anticipated not only because the method is contemplated but because the method will inherently lead to the treatment of the edema produced by the glioma. See Ex parte Novitski 26 USPQ 1389 (BPAI 1993).

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between

the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

12. Claims 1, 2, 8-10, 22 and 24-26 are rejected under 35 U.S.C. § 103 as being unpatentable over WO94/10202 as evidenced by Taber's Cyclopedic Medical Dictionary (1989, 16th Ed, F.A. Davis Company, Philadelphia, p.742) and Risau (Acta Neurochirurgica. Supplementum, 1994, 60:109-112) in view of 5,955,311 and US Patent No. 5,306,710.

The claims are drawn to a method of treating a mammal having edema, cerebral edema, comprising administering to said mammal an effective amount of hVEGF antagonist wherein said antagonist comprises an anti-VEGF antibody,

wherein the antibody is a monoclonal antibody, a chimeric antibody, a humanized antibody.

In order to facilitate compact prosecution, it is assumed for examination purposes that claims 8-10 are dependent upon claim 1 and that claims 24-26 are dependent upon claim 22.

Taber and Risau teach as set forth above.

WO94/10202 teaches as set forth above and further teaches that all antagonists of hVEGF that act by interfering with the binding of hVEGF to a cellular receptor shall be considered equivalent for the purposes of the invention (p. 4, lines 18-20) and that these antagonists include anti-VEGF and anti-VEGF receptor antibodies (p 4, lines 23-24) and that methods of administration of the antagonists include intratumoral, peritumoral, intralesional and perilesional route in order to exert local effects (p. 15, lines 5-10). WO94/10202 teach as set forth above but does not teach a method of treatment wherein the edema is cerebral edema.

US Patent No. 5,955,311 teaches a method of treating a mammal, wherein the mammal is a human (col 6, (lines 40-45), preferably having glioblastoma (col 6, lines 56-67) comprising administering an anti-VEGF receptor monoclonal antibody in order to block VEGF activation of the receptor in order to inhibit tumor growth (col 6, lines 12-, 21-24 and 46-67) (and teach that it has been demonstrated that blocking VEGF with neutralizing anti-VEGF antibodies results in the inhibition of the growth of human tumor glioblastoma xenografts in nude mice, as reported by Kim et al (col 2, lines 22-28) and teaches that high levels of VEGF receptors are expressed by endothelial cells that infiltrate gliomas and that VEGF receptor levels

are specifically upregulated by VEGF produced by human glioblastomas (col 2, lines 13-16) and teaches that humanized and chimeric antibodies are the functional equivalents of the antibodies of the invention (col 8, lines 62-67) and exemplifies the treatment of human glioblastoma with an anti-rat VEGF receptor antibody which is clearly a hVEGF antagonist as the human glioblastoma growth was clearly inhibited by the treatment (col 23, line 64-col 24, line 7).

US Patent No. 5,306,710 teaches that brain edema is a condition in which there is increased water content in brain tissues and that the medical conditions associated with brain edema include brain tumors (col 3, lines 53-66) and teaches that brain edema poses a serious medical emergency where the increased amounts of water compress and distort tissue architecture and impede delivery of oxygen to brain cells (col 4, lines 3-7).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to treat cerebral edema in a patient with glioblastoma, using the method of WO94/10202 by administering an anti-VEGF monoclonal antibody by any of the intratumoral, peritumoral, intralesional and perilesional routes, because WO94/10202 specifically teaches a method for the treatment of edema associated with brain tumor by administering an anti-VEGF monoclonal antibody and because US Patent No. 5,955,311 teaches that anti-VEGF activation therapy is effective for treating glioblastoma (a brain tumor characterized by edema) in a patient and because US Patent No. 5,306,710 specifically teaches that brain edema poses a serious medical emergency. One of ordinary skill in the art would have been motivated to treat cerebral edema in a patient with glioblastoma,

using the method of WO94/10202 by administering an anti-VEGF monoclonal antibody by any of the intratumoral, peritumoral, intralesional and perilesional routes because US Patent No. 5,306,710 specifically teaches that increased amounts of water impede delivery of oxygen to brain cells and treatment of the edema would be expected to facilitate delivery of oxygen to brain cells and reduce brain damage.

13. Claims 1, 2, 8-10, 22 and 24-26 are rejected under 35 U.S.C. § 103 as being unpatentable over US Patent No. 5,955,311, in view of US Patent No. 5,306,710 and WO94/10202 as evidenced by Taber's Cyclopedic Medical Dictionary (1989, 16th Ed, F.A. Davis Company, Philadelphia, p.742) and Risau (Acta Neurochirurgica. Supplementum, 1994, 60:109-112).

The claims are drawn to a method of treating a mammal having edema, cerebral edema, comprising administering to said mammal an effective amount of hVEGF antagonist wherein said antagonist comprises an anti-VEGF antibody, wherein the antibody is a monoclonal antibody, a chimeric antibody, a humanized antibody.

In order to facilitate compact prosecution, it is assumed for examination purposes that claims 8-10 are dependent upon claim 1 and that claims 24-26 are dependent upon claim 22.

US Patent No. 5,955,311 teaches as set forth above but does not teach a method of treating cerebral edema with an anti-VEGF antibody, monoclonal antibody, chimeric antibody, humanized antibody or teach a method of treating cerebral edema.

WO94/10202, Taber and Risau and US Patent No. 5,306,710 teach as set forth above.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to treat cerebral edema in a patient with glioblastoma, by substituting the anti-VEGF monoclonal antibody of WO94/10202 for the anti-VEGF receptor monoclonal antibody of US Patent No. 5,955,311 and by substituting the administrative routes of WO94/10202 into the method of US Patent No. 5,955,311 because WO94/10202 specifically teaches the equivalency of monoclonal antibodies against VEGF and VEGF receptor as antagonists for the treatment of brain tumors, including glioblastoma which is characterized by cerebral edema. Since US Patent No. 5,955,311 exemplifies the successful treatment of and reduction of the tumor and the tumor is known to be characterized by the production of edema, one of ordinary skill in the art would have expected to successfully treat the edema as a result of successful tumor treatment. One of ordinary skill in the art at the time the invention was made would have been motivated to treat cerebral edema in a patient with glioblastoma, using the method of the combined references because US Patent No. 5,306,710 specifically teaches that increased amounts of water impede delivery of oxygen to brain cells and treatment of the edema would be expected to facilitate delivery of oxygen to brain cells and reduce brain damage.

Further, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to substitute humanized or chimeric antibodies for a monoclonal antibody because US Patent No. 5,955,311 specifically teaches that humanized and chimeric antibodies are functional equivalents of the

monoclonal antibodies of the invention and because WO94/10202 specifically teaches that humanized and chimeric variants of the monoclonal antibody of the invention are included within the scope of the invention. One of ordinary skill in the art would have expected to successfully use the functional equivalents in the method of the combined references.

14. No claims allowed.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Ungar, PhD whose telephone number is (703) 305-2181. The examiner can normally be reached on Monday through Friday from 7:30am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached at (703) 308-3995. The fax phone number for this Art Unit is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Effective, February 7, 1998, the Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1642.

Susan Ungar
Primary Patent Examiner
June 2, 2000